

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"6884483"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L2	3	"5596123"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L3	12635	MADGE.in. DOLMAN.in. DEADMAN.in. KENNEDY.in. COMBE-MARZELLE.in. KAKKAR.in.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/01/26 11:28
L4	36	L3 and boronic	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/01/26 11:28
L5	11424	boronic acid	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L6	1805	L5 same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L7	370	L6 same pharmaceutically	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L8	299	L6 and thrombin	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L9	202	L7 and thrombin	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28

## EAST Search History

L10	202	L9 and inhibitor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L11	47	L10 and "564"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L12	47	L11 not L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L13	169	"5187157"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L14	11753	base addition salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L15	28	L14 same L5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L16	4	"5814622"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L17	225	548/405	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L18	220	L17 and acid	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L19	68	L17 and L5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28

## EAST Search History

L20	10	L19 and thrombin	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28
L21	18	L15 not L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	ON	2007/01/26 11:28

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NEWS 9 NOV 20     CA/CAplus to MARPAT accession number crossover limit increased  
                  to 50,000  
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NEWS 11 DEC 11    CAS REGISTRY chemical nomenclature enhanced  
NEWS 12 DEC 14    WPIDS/WPINDEX/WPIX manual codes updated  
NEWS 13 DEC 14    GBFULL and FRFULL enhanced with IPC 8 features and  
                  functionality  
NEWS 14 DEC 18    CA/CAplus pre-1967 chemical substance index entries enhanced  
                  with preparation role  
NEWS 15 DEC 18    CA/CAplus patent kind codes updated  
NEWS 16 DEC 18    MARPAT to CA/CAplus accession number crossover limit increased  
                  to 50,000  
NEWS 17 DEC 18    MEDLINE updated in preparation for 2007 reload  
NEWS 18 DEC 27    CA/CAplus enhanced with more pre-1907 records  
NEWS 19 JAN 08    CHEMLIST enhanced with New Zealand Inventory of Chemicals  
NEWS 20 JAN 16    CA/CAplus Company Name Thesaurus enhanced and reloaded  
NEWS 21 JAN 16    IPC version 2007.01 thesaurus available on STN  
NEWS 22 JAN 16    WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data  
NEWS 23 JAN 22    CA/CAplus updated with revised CAS roles  
NEWS 24 JAN 22    CA/CAplus enhanced with patent applications from India  
  
NEWS EXPRESS    NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT  
                  MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
                  AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.  
  
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DICTIONARY FILE UPDATES: 25 JAN 2007 HIGHEST RN 918475-45-3

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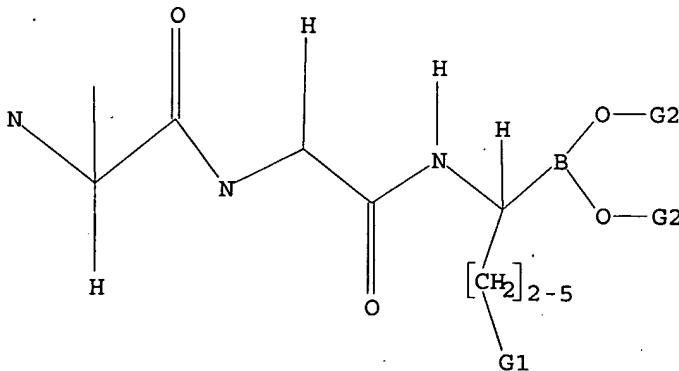
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## L1 STRUCTURE UPLOADED

=> d 11

## L1 HAS NO ANSWERS

## L1 STR



### G1 MeO, EtO, X, OH

G2 H, M

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 179 TO ITERATE

100.0% PROCESSED 179 ITERATIONS 4 ANSWERS  
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 2778 TO 4382  
PROJECTED ANSWERS: 4 TO 200

L2 4 SEA SSS SAM L1

=> s 11 full  
FULL SEARCH INITIATED 11:40:22 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 3292 TO ITERATE

100.0% PROCESSED 3292 ITERATIONS 44 ANSWERS  
SEARCH TIME: 00.00.01

L3 44 SEA SSS FUL L1

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COST IN U.S. DOLLARS SINCE FILE TOTAL  
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FULL ESTIMATED COST 172.10 172.31

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=> s 13  
L4 17 L3

=> s 13 not py > 2005  
17 L3  
1407318 PY > 2005  
L5 7 L3 NOT PY > 2005

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YOU HAVE REQUESTED DATA FROM 7 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2005:474929 CAPLUS  
 DOCUMENT NUMBER: 143:7986  
 TITLE: Method for synthesizing peptide boronic acids  
 INVENTOR(S): Walter, Armin; Olbrich, Alfred; Weiland-Waibel, Andrea  
 M. T.; Krimmer, Dieter  
 PATENT ASSIGNEE(S): Trigen Limited, UK  
 SOURCE: U.S. Pat. Appl. Publ., 43 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 6  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005119226	A1	20050602	US 2004-937181	20040908
US 2005282757	A1	20051222	US 2005-78097	20050309
PRIORITY APPLN. INFO.:			US 2003-501718P	P 20030909
			GB 2002-20764	A 20020909
			GB 2002-20822	A 20020909
			GB 2003-7817	A 20030404
			GB 2003-11237	A 20030516
			GB 2003-15691	A 20030704
			US 2003-658971	A2 20030909
			US 2003-659178	A2 20030909
			US 2003-659179	A2 20030909
			US 2004-937181	A2 20040908
			US 2004-937854	A2 20040908

OTHER SOURCE(S): MARPAT 143:7986

AB Organoboronic acids, e.g., Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub> (Mpg = 3-methoxypropylglycine residue; Cbz = benzyloxycarbonyl), are made by hydrolyzing their diethanolamine adducts under conditions which avoid substantial C-B bond breakage. The product acids are substantially free of degradation product derived from cleavage of the C-B bond and are converted into base addition salts for use in anti-thrombotic pharmaceutical formulations.

IT 667917-15-9P 667917-16-0P 667917-82-0P

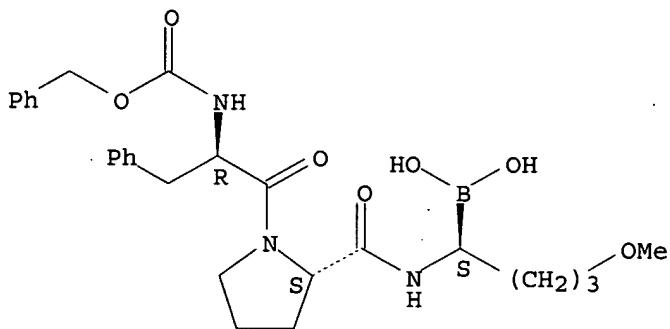
852457-84-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (synthesis of peptide boronic acids via cleavage of diethanolamine adducts)

RN 667917-15-9 CAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, calcium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

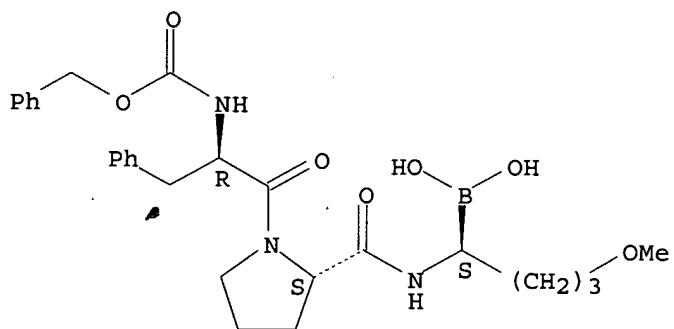


● x Ca

RN 667917-16-0 CAPLUS

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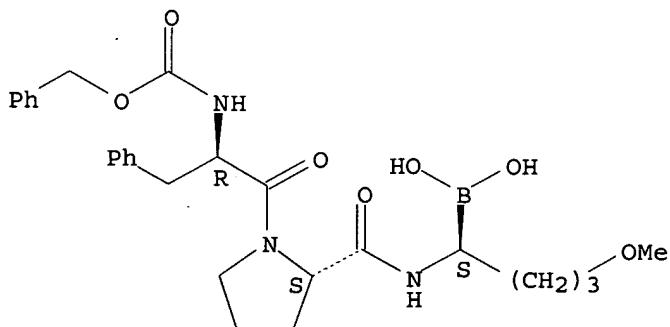
Absolute stereochemistry.



RN 667917-82-0 CAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, sodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



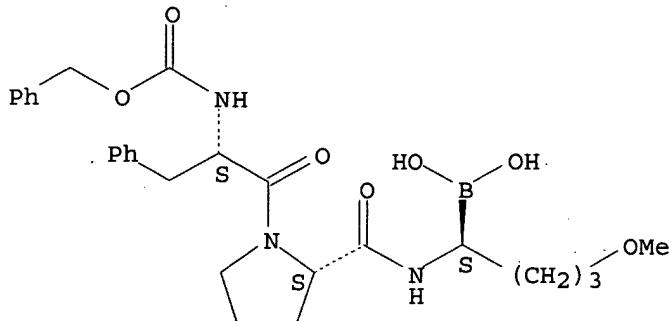
● x Na

RN 852457-84-2 CAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-phenylalanyl-N-[(1S)-1-borono-

4-methoxybutyl] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:605764 CAPLUS

DOCUMENT NUMBER: 129:341097

TITLE: Bifunctional Peptide Boronate Inhibitors of Thrombin: Crystallographic Analysis of Inhibition Enhanced by Linkage to an Exosite 1 Binding Peptide

AUTHOR(S): Skordalakes, Emmanuel; Elgendi, Said; Goodwin, Christopher A.; Green, Donovan; Scully, Michael F.; Kakkar, Vijay V.; Freyssinet, Jean-Marie; Dodson, Guy; Deadman, John J.

CORPORATE SOURCE: Peptide Synthesis Section and Biochemistry Section, Thrombosis Research Institute, London, SW3 6LR, UK

SOURCE: Biochemistry (1998), 37(41), 14420-14427

CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The affinity of the hirudin49-64 segment for exosite 1 of thrombin has been used previously to enhance the potency of simple competitive inhibitors [DiMaio, J., Gibbs, B., Munn, D., Lefebvre, J., Ni, F., Konishi, Y. (1990) J. Biol. Chemical 265, 21698-21703, and Maraganore, J. M., Bourdon, P., Jablonski, J., Ramachandran, K. L., and Fenton, J. W., II (1990) Biochem. 29, 7095-7087]. Using a similar approach, we have enhanced the activity of two active site directed thrombin inhibitors by attaching this segment via a novel reverse oriented linker to each of two tripeptide boronate inhibitors. At P1, compound 1 contains an arginine-like, isothiouronium, side chain, while compound 2 contains an uncharged, bromopropyl residue. Inhibition of human  $\alpha$ -thrombin by compound 1 shows slow, tight-binding competitive kinetics (final  $K_i$  of  $2.2 \text{ pM}$ ,  $k_1$  of  $3.51 \pm 10^7 \text{ M}^{-1} \text{ s}^{-1}$ , and  $k_{-1}$  of  $1.81 \pm 10^{-4} \text{ s}^{-1}$ ). The addition of hirugen peptide ( $20 \mu\text{M}$ ) competes for exosite 1 binding and restores the  $k_1$  and  $k_{-1}$  to that of the analogous tripeptide,  $0.29 \pm 10^7 \text{ M}^{-1} \text{ s}^{-1}$  and  $0.13 \pm 10^{-4} \text{ s}^{-1}$ , resp. Compound 1 has enhanced specificity for thrombin over trypsin with  $K_i$  Try/KiThr of apprx. 900 compared to the analogous tripeptide, with  $K_i$  Try/KiThr of apprx. 4. Compound 2 acts as a competitive inhibitor ( $K_i$  Thr of  $0.6 \text{ nM}$ ) and is highly selective with no effect on trypsin. Crystallog. anal. of complexes of human  $\alpha$ -thrombin with compound 1 ( $1.8 \text{ \AA}$ ) and compound 2 ( $1.85 \text{ \AA}$ ) shows a covalent bond between the boron of the inhibitor and Ser195 (bond lengths B-O of  $1.55$  and  $1.61 \text{ \AA}$ , resp.). The isothiouronium group of compound 1 forms bidentate interactions with Asp189. The P2 and P3 residues of the inhibitors form interactions with the S2 and S3 sites of thrombin similar to other D-Phe-Pro based inhibitors [Bode, W., Turk, D., and Karshikov, A. (1992) Protein Sci. 1, 426-471.]. The linker exits the active site cleft of thrombin forming no interactions,

while the binding of Hir49-64 segment to exosite 1 is similar to that previously described for hirudin [Rydel, T. J., Tulinsky, A., and Bode, W. (1991) J. Mol. Biol. 221, 583-601]. Because of the similarity of binding at each of these sites to that of the analogous peptides added alone, this approach may be used to improve the inhibitory activity of all types of active site directed thrombin inhibitors and may also be applicable to the design of inhibitors of other proteases.

IT 143718-39-2

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

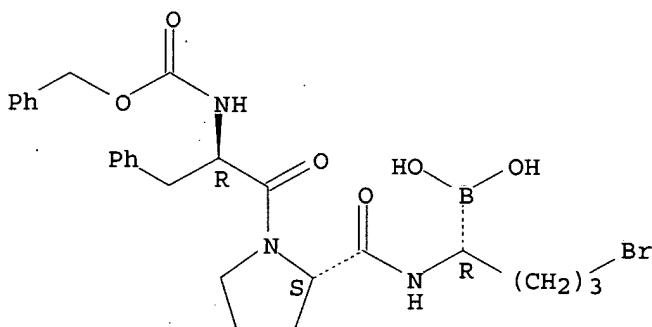
(bifunctional peptide boronate inhibitors of thrombin, crystallog.

anal. of inhibition enhanced by linkage to exosite 1 binding peptide)

RN 143718-39-2 CAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-bromobutyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 215509-98-1

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(bifunctional peptide boronate inhibitors of thrombin, crystallog.

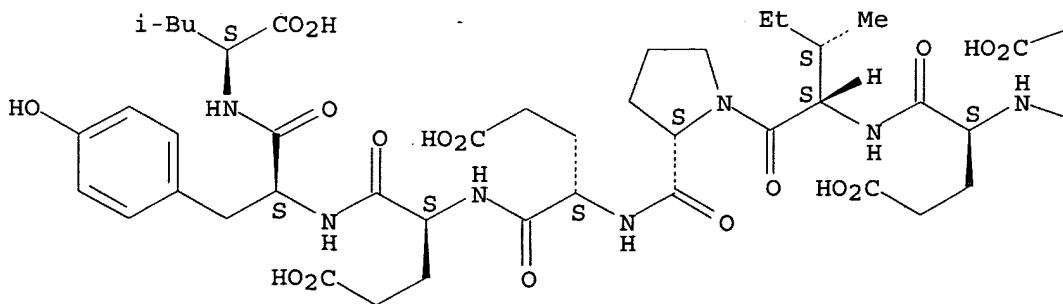
anal. of inhibition enhanced by linkage to exosite 1 binding peptide)

RN 215509-98-1 CAPLUS

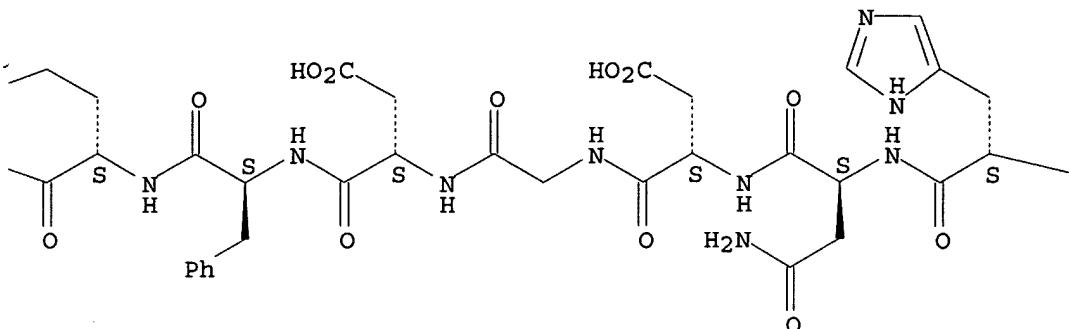
CN L-Leucine, N-(4-carboxy-1-oxobutyl)glycylglycyl-L-glutaminyl-L-seryl-L-histidyl-L-asparaginyl-L- $\alpha$ -aspartylglycyl-L- $\alpha$ -aspartyl-L-phenylalanyl-L- $\alpha$ -glutamyl-L- $\alpha$ -glutamyl-L-isoleucyl-L-prolyl-L- $\alpha$ -glutamyl-L- $\alpha$ -glutamyl-L-tyrosyl-, (1 $\rightarrow$ 1')-amide with D-phenylalanyl-N-[(1R)-1-borono-4-bromobutyl]-L-prolinamide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

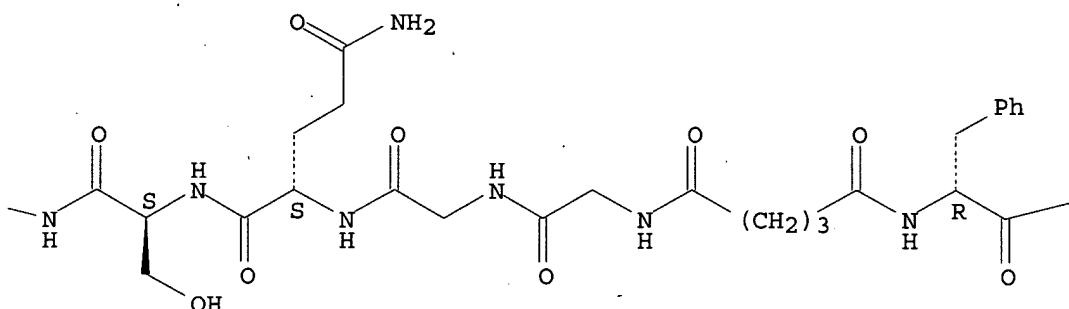
PAGE 1-A



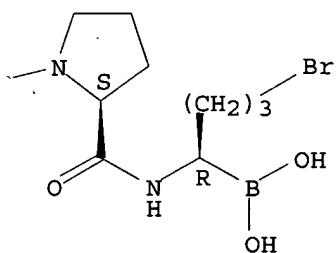
PAGE 1-B



PAGE 1-C



PAGE 1-D



REFERENCE COUNT:

42

THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:352865 CAPLUS

DOCUMENT NUMBER: 129:54603

TITLE: Preparation of antiviral peptide derivatives

INVENTOR(S): Attwood, Michael Richard; Hurst, David Nigel; Jones, Philip Stephen; Kay, Paul Brittain; Raynham, Tony Michael; Wilson, Francis Xavier

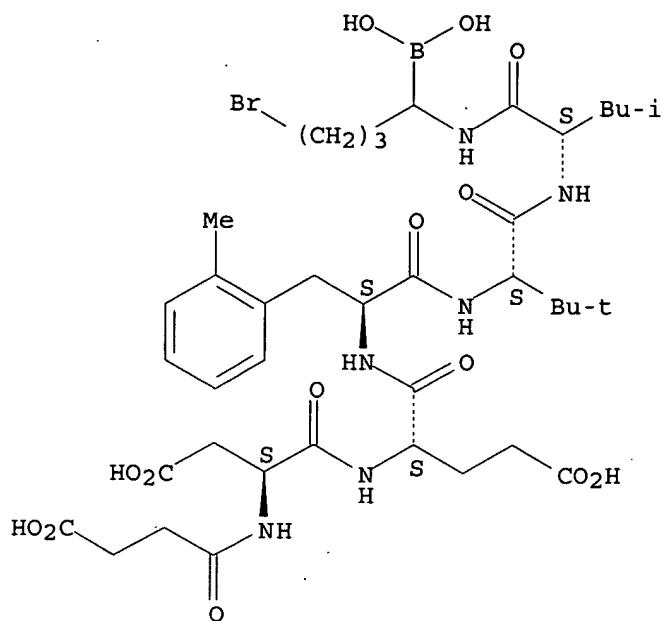
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.  
 SOURCE: PCT Int. Appl., 132 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822496	A2	19980528	WO 1997-EP6189	19971107
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
IN 1997MA02398	A	20050304	IN 1997-MA2398	19971023
CA 2271288	A1	19980528	CA 1997-2271288	19971107
AU 9855510	A	19980610	AU 1998-55510	19971107
EP 941233	A2	19990915	EP 1997-951869	19971107
R: DE, ES, FR, GB, IT				
JP 2000508344	T	20000704	JP 1998-523153	19971107
JP 3372260	B2	20030127		
ZA 9710156	A	19980518	ZA 1997-10156	19971111
US 5866684	A	19990202	US 1997-971036	19971114
US 6018020	A	20000125	US 1998-96570	19980612
PRIORITY APPLN. INFO.:			GB 1996-23908	A 19961118
			WO 1997-EP6189	W 19971107
			US 1997-971036	A3 19971114

OTHER SOURCE(S): MARPAT 129:54603

- AB Peptides R9NHCHR8CONHCHR7CONR6CHR5CONHCHR4CONR3CHR2CONHCHRR1 [R = CHO or B(OH)<sub>2</sub>; R1 = optionally substituted alkyl, alkenyl, alkynyl; R2 = optionally substituted alkyl; R3 = H, alkyl; or R2 and R3 together represent di- or trimethylene optionally substituted by hydroxy; R4 = optionally substituted alkyl, alkenyl, aryl, cycloalkyl; R5 = optionally substituted alkyl, cycloalkyl; R6 = H, alkyl; R7 = optionally substituted alkyl, cycloalkyl; R8 = optionally substituted alkyl; R9 = alkylcarbonyl, carboxyalkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, alkoxy carbonyl, arylalkoxy carbonyl] or their salts were prepared for use as antiviral agents. Thus, 2(RS)-[[N-[N-[N-[N-(3-carboxypropionyl)-L- $\alpha$ -aspartyl]-L- $\alpha$ -glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenaldehyde, prepared via intermediate N-[N-[N-[N-[N-(3-tert-butoxycarbonyl)propionyl]-O-tert-butyl-L- $\alpha$ -aspartyl]-O-tert-butyl-L- $\alpha$ -glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, was assayed for inhibition of ACV protease (IC<sub>50</sub> = 0.09  $\mu$ Mol/l).
- IT 208520-48-3P 208520-64-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of antiviral peptide derivs.)
- RN 208520-48-3 CAPLUS  
 CN L-Leucinamide, N-(3-carboxy-1-oxopropyl)-L- $\alpha$ -aspartyl-L- $\alpha$ -glutamyl-2-methyl-L-phenylalanyl-3-methyl-L-valyl-N-(1-borono-4-bromobutyl)-(9CI) (CA INDEX NAME)

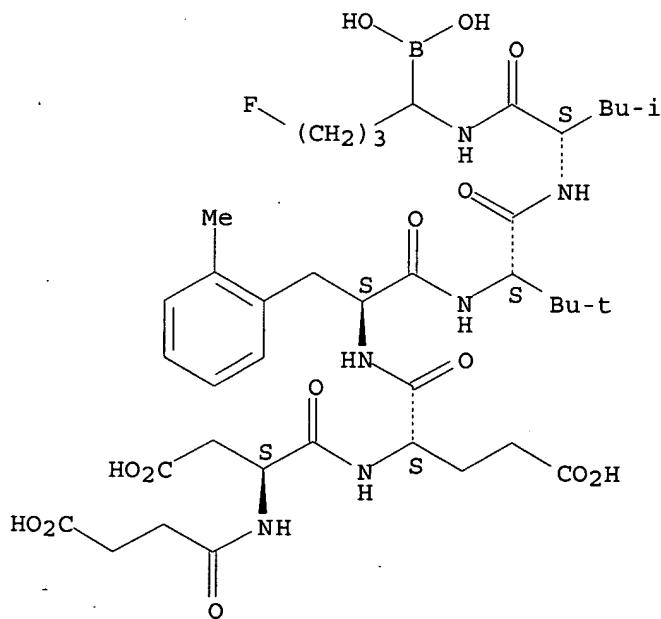
Absolute stereochemistry.



RN 208520-64-3 CAPLUS

CN L-Leucinamide, N-(3-carboxy-1-oxopropyl)-L- $\alpha$ -aspartyl-L- $\alpha$ -glutamyl-2-methyl-L-phenylalanyl-3-methyl-L-valyl-N-(1-borono-4-fluorobutyl)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:667172 CAPLUS

DOCUMENT NUMBER: 127:244735

TITLE: Crystallographic Structures of Human  $\alpha$ -Thrombin Complexed to Peptide Boronic Acids Lacking a Positive Charge at P1. Evidence of Novel Interactions  
Skordalakes, Emmanuel; Tyrell, Richard; Elgendi, Said;  
Goodwin, Christopher A.; Green, Donovan; Dodson, Guy;

AUTHOR(S):

CORPORATE SOURCE: Scully, Michael F.; Freyssinet, Jean-Marie H.; Kakkar, Vijay V.; Deadman, John J.  
SOURCE: Thrombosis Research Institute, London, SW3 6LR, UK  
Journal of the American Chemical Society (1997),  
119(41), 9935-9936  
CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Moc-Dpa-Pro-boroMpg, compound (I), lacking a pos. charge at P1 is a potent inhibitor of human  $\alpha$ -thrombin (H $\alpha$ T) (KiThr = 3nM). The crystallog. anal. of the enzyme:inhibitor complex of I at 1.9 $\text{\AA}$  resolution, provides for the first time a partial explanation for the basis of the high affinity interaction at the S1 site. Tripeptide boronates I and Z-Dpa-Pro-boroVal, compound (II), were synthesized as described, and crystals obtained for I and II with H $\alpha$ T and N-Ac-hirugen. Crystals were flash cooled and data sets were collected to a maximum Bragg spacing of 1.8 $\text{\AA}$  and 2.1 $\text{\AA}$  resp. and subsequently processed with Denzo and Scalepack and AMORE (H $\alpha$ T.hirugen.PPACK). The data was further refined using Spartan, Refmac and ARP. Refinement converged to a crystallog. R factor of 17.5% (Rfree = 24.0%, using 5% of reflections) and 17.0% (Rfree = 23.5%) and R-factors were 0.32 and 0.36, and RMS deviations were 0.02 $\text{\AA}$  and 2.4°, and 0.019 $\text{\AA}$  and 2.5° for the complex with I and II, resp. Atomic coordinates have been deposited in the Brookhaven Protein Data Bank. Both compound I and II form the canonical interactions with human  $\alpha$ -thrombin at the S2 and S3 sites, already shown with the PPACK complex. Complex I shows the expected covalent interaction of c.a. 1.75 $\text{\AA}$  between the boron and the Ser-195O $\gamma$  of the H $\alpha$ T and O1B is coordinated by Gly-193NH and Ser-195NH in the so called oxy-anion pocket (Figure 1) (O1B-193GlyNH 2.79 $\text{\AA}$ , O1B-ser195NH 3.11 $\text{\AA}$ ). In complex I, the ether oxygen is functioning as a hydrogen bond acceptor from a water (2.54  $\text{\AA}$ ) which is, in turn, bridging to Gly-216CO and Gly-219CO. This bridging interaction has previously been observed in the fibrinopeptide A -  $\alpha$ -thrombin complex, between the  $\epsilon$ -NH of the arginine guanidino, WAT80 and Gly219CO. Surprisingly, despite the reasonable affinity of compound II, (KiThr 20nM), crystallog. anal. at 2.1 $\text{\AA}$  of the complex II shows a novel interaction where the boron is 3.34 $\text{\AA}$  from Ser-195O $\gamma$ , and the boron oxygen O1B is now displaced from the oxyanion pocket and is hydrogen bonded (2.84 $\text{\AA}$ ) to Ser-195O $\gamma$ . The displacement allows O1A to interact more strongly with the carboxylate side chain of Glu-192 (O1A-Glu192OE1 3.11 $\text{\AA}$  compared to 4.16 $\text{\AA}$  for complex II and I resp.). The inhibitor P1 valine-like iso-Pr side chain in complex II is displaced into close proximity with Val-213 of H $\alpha$ T. The discovery of this interaction between S1 and S3 for human  $\alpha$ -thrombin may provide a better understanding for the design of low mol. weight inhibitors of high specificity.

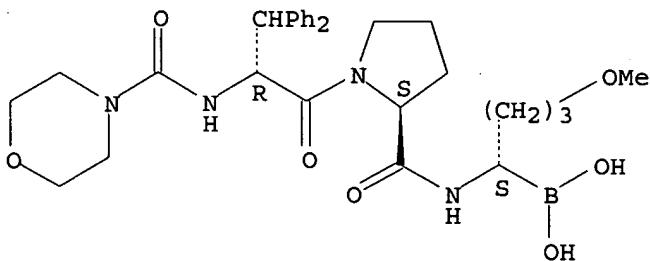
IT 195703-51-6

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(crystallog. structures of Human  $\alpha$ -thrombin complexed to peptide boronic acids)

RN 195703-51-6 CAPLUS

CN L-Prolinamide, N-(4-morpholinylcarbonyl)- $\beta$ -phenyl-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1995:792582 CAPLUS  
 DOCUMENT NUMBER: 123:199408  
 TITLE: Preparation of peptide derivatives of boronic acid and pharmaceutical compositions containing them  
 INVENTOR(S): de Nanteuil, Guillaume; Lila, Christine; Laubie, Michel; Verbeuren, Tony; Simonet, Serge; Rupin, Alain; Portevin, Bernard  
 PATENT ASSIGNEE(S): Adir et Cie., Fr.  
 SOURCE: Can. Pat. Appl., 37 pp.  
 CODEN: CPXXEB  
 DOCUMENT TYPE: Patent  
 LANGUAGE: French  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2116181	A1	19940825	CA 1994-2116181	19940222
FR 2701951	A1	19940902	FR 1993-2082	19930224
FR 2701951	B1	19950609		
AU 9456302	A	19940901	AU 1994-56302	19940222
AU 666801	B2	19960222		
US 5444049	A	19950822	US 1994-199473	19940222
JP 06298795	A	19941025	JP 1994-25245	19940223
JP 2533290	B2	19960911		
EP 615978	A1	19940921	EP 1994-400393	19940224
EP 615978	B1	19990512		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
ZA 9401273	A	19941019	ZA 1994-1273	19940224
AT 179988	T	19990515	AT 1994-400393	19940224
ES 2133504	T3	19990916	ES 1994-400393	19940224
HK 1010378	A1	20000428	HK 1998-111350	19981020
PRIORITY APPLN. INFO.:			FR 1993-2082	A 19930224

OTHER SOURCE(S): MARPAT 123:199408  
 AB R1NHCR2R2'COA CONHCOR3B(OR4)(OR5) [R1 = H, acyl, alkyl, benzyl, alkoxy carbonyl, benzyl oxy carbonyl, phenoxy carbonyl, 5-[dimethylamino]naphthylsulfonyl], alkoxy carbonyl methyl, carboxymethyl; R2 = H, Ph, (un)substituted benzyl, 3-thienylmethyl, 2-pyridinylmethyl, diphenylmethyl, fluorenyl, naphthylmethyl, benzocyclobutyl, dicyclopropylmethyl, Me, indanyl, cycloalkylmethyl; R2' = H, benzyl; R2R2' = PhCH:; R3 = alkyl, guanidinophenyl, amidinophenyl, aminophenyl, guanidinobenzyl, amidinobenzyl, aminobenzyl, cycloalkyl; R4, R5 = H, alkyl; B(OR4)(OR5) = boronic ester of pinanediol; A represents a group such as perhydroindole, 2-azabicyclo[2.2.2]octane, 2-azabicyclo[3.3.0]octane, 2-azabicyclo[2.2.1]heptane, perhydroisoindole, indoline, isoindoline, perhydroquinoline, perhydroisoquinoline, etc.] were prepared as thrombin inhibitors. E.g., peptidic coupling of Phi-OBz [Phi = (2S,3aS,7aS)-perhydroindole-2-carbonyl] and Ac-(R)Phe-OH, followed by hydrogenolysis and reaction with N-hydroxysuccinimide, gave

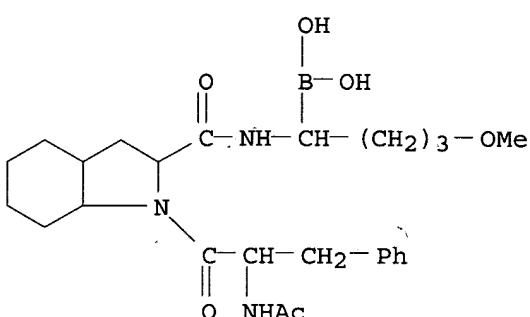
Ac-(R,S)Phe-Phi-OSuc (Suc = succinimido). The latter was treated with (+)- $\alpha$ -pinanediol (R)-1-amino-4-bromobutylboronate hydrochloride to give (+)- $\alpha$ -pinanediol 1-(R)-[(Ac-(R,S)Phe-Phi)amino]-4-bromobutylboronate. The latter was treated with NaN<sub>3</sub>, then hydrogenated, reacted with cyanamide and then with BC13 to give 1-(R)-[(Ac-(R,S)Phe-Phi)amino]-4-guanidinobutylboronic acid acetate (I). The concentration of I necessary to double blood clotting time was less than that required of a reference compound (DUP 714).

IT 167843-12-1P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and thrombin inhibiting activity of peptide derivs. of boronic acid)

RN 167843-12-1 CAPLUS

CN Boronic acid, [1-[[[1-[2-(acetylamino)-1-oxo-3-phenylpropyl]octahydro-1H-indol-2-yl]carbonyl]amino]-4-methoxybutyl] - (9CI) (CA INDEX NAME)



L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:629678 CAPLUS

DOCUMENT NUMBER: 123:106238

TITLE: Episelection: Novel Ki .apprx. Nanomolar Inhibitors of Serine Proteases Selected by Binding or Chemistry on an Enzyme Surface

AUTHOR(S): Katz, Bradley A.; Finer-Moore, Janet; Mortezaei, Reza; Rich, Daniel H.; Stroud, Robert M.

CORPORATE SOURCE: Arris Pharmaceutical Corporation, South San Francisco, CA, 94080, USA

SOURCE: Biochemistry (1995), 34(26), 8264-80  
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 123:106238

AB A novel class of mechanism-based inhibitors of the serine proteases is developed using epitaxial selection. Tripeptide boronates esterified by an alc. or alc's. at the boron retain the tight binding to trypsin-like enzymes associated with transition-state analogs and incorporate addnl. groups that can be utilized for selectivity between proteases. Formed by reaction of a series of alc's. with the inhibitor boronate oxygen(s), the most structurally compatible alc.-derivatized inhibitors are either selected by binding to the enzyme (epitaxial selection) or assembled by epitaxial reaction on the enzyme surface. Mass spectrometry of the derivatized boronates and x-ray crystallog. of the complexes identify the chemical structures and the three-dimensional interactions of inhibitors generated. This scheme also engineers novel, potent (Ki .apprx. 7 nM), and more specific inhibitors of individual serine proteases, by derivitizations of compds. obtained by epitaxial selection.

IT 165617-42-5P

RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC

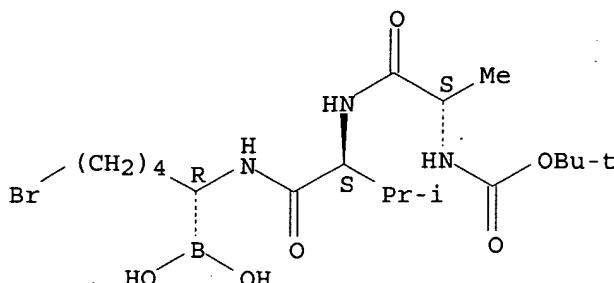
## (Process)

(synthesis, crystal structure and binding of novel inhibitors of serine proteases selected by binding or chemical on enzyme surface)

RN 165617-42-5 CAPLUS

CN L-Valinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-(1-borono-5-bromopentyl)-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1992:572073 CAPLUS

DOCUMENT NUMBER: 117:172073

TITLE:

New peptide boronic acid inhibitors of thrombin  
Elgendi, Said; Deadman, John; Patel, Geeta; Green,  
Donovan; Chino, Naoyoshi; Goodwin, Christopher A.;  
Scully, Michael F.; Kakkar, Vijay V.; Claeson, Goran

CORPORATE SOURCE:

Thrombosis Res. Inst., London, SW3 6LR, UK

SOURCE:

Tetrahedron Letters (1992); 33(29), 4209-12

CODEN: TELEAY; ISSN: 0040-4039

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Synthetic peptides PhCH2O2C-D-Phe-Pro-NHCHR<sub>1</sub>2 [R = (CH<sub>2</sub>)<sub>3</sub>SC(NH<sub>2</sub>):NH<sub>2+</sub>, (CH<sub>2</sub>)<sub>3</sub>OMe, (CH<sub>2</sub>)<sub>4</sub>Me, CMe<sub>2</sub>Et, CH<sub>2</sub>Ph, (CH<sub>2</sub>)<sub>3</sub>Br, (CH<sub>2</sub>)<sub>7</sub>Me, 2-(2-dioxolanyl)ethyl; (OR<sub>1</sub>)<sub>2</sub> = pinanediol diester, pinacol diester] containing a P1 aminoboronic acid with a neutral side chain show good thrombin inhibition as well as selectivity for thrombin, and have no serious side effect on blood pressure.

IT 143718-39-2DP, pinanediol or pinacol diesters

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and thrombin inhibitory activity of)

RN 143718-39-2 CAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-bromobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

